## REMARKS

This amendment is in response to the Office Action dated March 16, 2006.

Claims 16-18 and 19-21 have been added to claim particular dosage ranges for the controlled-release and sustained-release dosages in claims 9 and 15, respectively. Allowance of all pending claims is respectfully requested.

Applicants respectfully contend that the rejection of claims 9 and 15 under the provisions of 35 U.S.C. 103(a) as obvious over Husbands et al (US 4,761,501) in view of Theeuwes (US 4,111,201) is traversed. The rejection is traversed for the following reasons relating to the limitations of the claims to a particular drug species, venlafaxine. First, Theeuwes does not teach a controlled-release and sustained-release dosage of venlafaxine because Theeuwes only teaches increasing the amount of drug delivered whereas venlafaxine would require decreasing drug delivery in order to work in a controlled-release and sustained-release dosage. Second, Theeuwes does not teach "successful[ly] maintaining substantially constant drug levels in the blood or in a tissue," which is required by a controlled-release dosage, because the expected premature release profile of venlafaxine would not maintain a substantially constant venlafaxine level in the Theeuwes form. Third, Theeuwes does not teach a sustained-release dosage of venlafaxine because there is no evidence that venlafaxine could be delivered with the 15 hour delivery dose profile disclosed in Theeuwes or that the Theeuwes delivery profile would be sufficient to deliver venlafaxine "within a therapeutic range" over that extended period of time. Fourth, there is no evidence that the relatively small dosage of highly soluble venlafaxine in Husbands et al. could be adapted to operate properly in the Theeuwes dosage form. Fifth, the unique properties of the venlafaxine species in claims 9 and 15 would suggest to a person skilled in the art that venlafaxine would not be an acceptable candidate for a controlled-release or

sustained-release dosage. Accordingly, claims 9 and 15 are not obvious over Husbands et al. in view of Theeuwes. Claims 16-21, as claims depending from claims 9 and 15, are also not obvious for the same reasons.

### A. Theeuwes Does Not Teach A Controlled-Release And Sustained-Release Dosage of Venlafaxine As Required By Claims 9 And 15

Applicants respectfully contend that Husbands in view of Theeuwes does not teach how to use a drug with the properties of venlafaxine in a controlled-release or sustained-release dosage. Theeuwes is concerned with agents having properties that "make it difficult to deliver substantially all of the agent" through a controlled- or sustained-release form. ('201 at col. 1:63-65). Although the drugs at issue in Theeuwes begin with a desirable zero order rate, their delivery rate soon changes to declining parabolic shape such that the drug remaining in the dosage form would be delivered too slowly. (*Id.*). Theeuwes' solution to the problem of insufficient drug delivery is a method to "***increase*** the amount of agent delivered" by extending the zero-order delivery and eliminating the declining parabolic delivery. ('201 at Col. 2:1-6 (emphasis added)). Theeuwes' solution assumes that all drugs, regardless of solubility, need ***more*** drug delivered because they are delivered too slowly over an extended duration. (*See id.*).

Theeuwes does not recognize that certain drugs, particularly venlafaxine, suffer from the opposite problem, namely that the drug's properties may cause the drug to be delivered prematurely. The drug in claims 9 and 15, venlafaxine, has a very high solubility and driving force that would be expected to lead to the ***premature*** release of venlafaxine in a controlled-release or sustained-release dosage, primarily as a result of convection motion in and hydrostatic pressure. (page 4:6-13). The premature release would result in too much drug being delivered too quickly and therefore a controlled-release or sustained-release dosage of venlafaxine would require ***decreasing*** the drug delivery rate. Therefore, Theeuwes' solution of an ***increased*** drug

delivery does not teach using a controlled-release or sustained-release form for venlafaxine that requires a ***decreased*** delivery rate.

The disclosure of a "suspending agent" in Theeuwes likewise does not teach a controlled-release or sustained-release dosage of venlafaxine. Theeuwes discloses mixing a suspending agent with the beneficial agent to deliver the beneficial agent "at concentrations ***greater*** than its saturation concentration in the fluid." ('201 col. 4:47-49 (emphasis added)). Theeuwes intends for the suspending agent to suspend an insoluble drug to allow increased delivery of the drug. (*See, e.g.*, '201 col. 4:50-55, 12:8-14). For example, Theeuwes discloses hydroxyethylcellulose as an agent to suspend an insoluble drug to allow increased delivery. Theeuwes never provides any basis or suggestion for using a suspending agent to be used with a highly soluble drug to ***decrease*** the delivery rate. On the other hand, Applicants use hydroxethylcellulose to change the properties of the solution containing the highly soluble venlafaxine so as to decrease the drug delivery rate. Therefore, combining Theeuwes with Husbands would fail to teach a controlled-release or sustained-release dosage form of venlafaxine in claims 9 and 15.

### B. Theeuwes In View Of Husbands Does Not Teach A Controlled-Release Dosage of Venlafaxine As Required By Claim 9

Applicants respectfully contend that there is also no evidence that the disclosure in Theeuwes would teach a controlled-release dosage of venlafaxine in claim 9. "Controlled-release" is defined as "successful[ly] maintaining substantially constant drug levels in the blood or in a tissue." (page 7:19-21). As explained above, merely putting venlafaxine in a controlled-release dosage described by Theeuwes would result in a premature release of the drug, not a "substantially constant drug level."

Furthermore, Theeuwes' only example of a release rate demonstrates a widely varied release rate ranging from over 20 mg/hr to below 10 mg/hr. ('201 at Fig. 7). Because of the

specific properties of venlafaxine, there is no evidence that it would have the same delivery profile when placed in the dosage form taught by Theeuwes. Furthermore, there is no evidence in Theeuwes that the release rate and profile demonstrated by Theeuwes would result in a "substantially constant [venlafaxine] level in the blood or in tissue." Applicants, on the other hand, provide examples that demonstrate the release of between 53 and 77 mg of venlafaxine at a controlled, zero-order rate. (page 21:6-28). Therefore, there is no evidence of a "reasonable expectation of success" that venlafaxine disclosed in Husbands could be used in the controlled-release delivery method disclosed in Theeuwes. *See Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, inc.*, 231 F.3d 1339, 1345 (Fed.Cir. 2000).

### C. Theeuwes In View Of Husbands Does Not Teach A Sustained-Release Dosage of Venlafaxine As Required By Claim 15

Applicants respectfully contend that merely disclosing delivery of a drug over "the same period of time," namely 15 hours, is insufficient to satisfy the definition of "sustained release." Applicants defined sustained release as not only delivery "over an extended period of time" but also delivery of the drug at drug levels "within a therapeutic range" over that extended period of time. (page 7:23-26). Theeuwes discloses delivering 235 mg of an antiarrhythmic drug, procainamide hydrochloride, over a 15 hour time period at a varying rate exceeding 20 mg/hr before eventually declining below 10 mg/hr. ('201 at col. 19:11-18, Fig. 7). There is no evidence that the Theeuwes delivery profile (either the delivery rate or the variance in the delivery rate) would be suitable for venlafaxine such that delivering venlafaxine at that rate would fall "within a therapeutic range." In fact, Applicants' examples would tend to show that the delivery profile disclosed in Theeuwes does not teach a sustained release dosage of venlafaxine. Applicants' examples disclose delivering 57 to 73 mg of venlafaxine hydrochloride at a controlled or zero-order rate over 15 to 20 hours. (page 21:6-28). The average delivery rate

for these examples is between 3.6 and 4.8 mg/hr, which would be less than half of the average delivery rate disclosed in Theeuwes. Therefore, there is no evidence of that venlafaxine disclosed in Husbands could be used in the sustained-release delivery method disclosed in Theeuwes.

### D. There Is No Evidence That The Dosage Of Highly Soluble Venlafaxine in Husbands Et Al. Could Be Adapted To The Dosage In Theeuwes

Applicants respectfully contend that there is no evidence that the dosage for venlafaxine disclosed in Husbands would be expected to work in the form disclosed in Theeuwes. In Husbands, the appropriate oral dose for a human is "from about 2 to about 50 milligrams." ('501 at col. 10: 25-27). In Theeuwes, the only release rate example releases 235 mg of procainamide hydrochloride at a rate beginning at over 20 mg/hour before eventually decreasing to under 10 mg/hr. ('201 at Fig. 7, col. 19:17-25). Using the rate disclosed in Theeuwes, the maximum 50 mg dose of venlafaxine disclosed in Husbands et al. would be fully released in a little over two hours, which would not be categorized as either controlled-release or sustained release. Theeuwes does not demonstrate or even assert that a small 50 mg dose of a highly soluble such as venlafaxine could be released at a substantially constant level or within a therapeutic range over an extended period of time. Instead, Theeuwes effectively presumes that a highly soluble drug would not need to be released at a rate slower than the rate dictated by its solubility and driving force because, as explained above, Theeuwes fails to teaches the ability to reduce the delivery rate of a highly soluble drug. Theeuwes recognizes its limited use for highly soluble agents by limiting its examples to soluble and insoluble agents. (*See* '201 at col. 11:64-66).

Applicants, on the other hand, demonstrate that a highly soluble drug having a premature delivery problem could be delivered in a controlled-release and sustained-release form. Using a venlafaxine dosage of 57 mg, which is similar to the dosage disclosed in Husbands et al.,

Applicants demonstrated that an acceptable dosage of venlafaxine could be released at a zero order rate over a period of 15 hours. (page 21:25-28). Applicants also demonstrate that dosages of 73 mg of venlafaxine could be released in a controlled manner over an extended period of 20 hours. (page 22:7-10). Theeuwes never demonstrates releasing a dosage less than almost five time the highest dosage disclosed in Husbands et al. Therefore, there is no evidence of a "reasonable expectation of success" that the venlafaxine, at the dosages disclosed in Husbands, could be used in the form disclosed in Theeuwes.

**E. The Unique Properties Of Venlafaxine Support Patentability**

As previously submitted in detail in Appellants' Brief from prior 2002-1138 appeal, and as attached and incorporated by reference, venlafaxine's unique properties would suggest to one skilled in the art that it would not be an acceptable candidate for controlled or sustained delivery. The particular drug species in the claims at issue, venlafaxine, possesses unique properties that differentiate it from other antidepressants when it comes to designing controlled-release or sustained-release drugs. Venlafaxine possesses a very high solubility and driving force that may lead to a premature release of venlafaxine, or venlafaxine may leak prematurely and overdose from a metered-dose delivery form, such as that disclosed in Theeuwes.

As further detailed in the previously submitted brief, the high solubility and driving force values for venlafaxine indicate that this particular drug is prone to rapid dissolution into an aqueous media when subject to a convective flow of water and so achieving a controlled delivery rate of venlafaxine in a turbulent, aqueous environment, such as in the churning gastrointestinal tract, would be problematic. Moreover, the high driving force would argue for dose dumping and uncontrolled leaching of the drug from a dosage form that attempts to meter the delivery of this drug at a controlled rate. Theeuwes does not recognize that highly soluble drugs, or any

drugs for that matter, could be subject to such problems and therefore does not suggest any resolution.

Moreover, the relatively small dosage form of venlafaxine further amplifies the effect of its high solubility and driving force properties in the convective environment of the intestines. The current proscribed dose of venlafaxine is about 37.5-150 mg per day, which is equivalent to a delivery rate of only 1.6 to 6 mg per hour. Therefore, small perturbations in the flow of aqueous fluids about the orifice can produce high and uncontrolled convective-flow effects. For example, as little as a ten microliter pulse of fluid directed toward the orifice from the external environment when the dosage form is in operation would sweep out 5.7 mg of drug by convection. This convective-induced pulse of drug, which is at the upper end of one full-hour dose, would be added to the amount of drug delivered by hydro-osmotic pumping action. The uncontrolled convective-flow effects that would result from the normal churning and peristaltic action of the gastrointestinal tract would predict an ***uncontrolled*** and ***highly variable***, non-constant release of this drug, especially where there is a small dose and a high driving force.

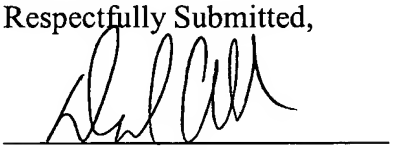
The point is that venlafaxine possesses an extremely high solubility and driving force that, upon analysis by one skilled in the art at the time of the invention, would have suggested to a skilled artisan that venlafaxine would not be acceptable for controlled or sustained delivery. As set forth in the present application at page 4, lines 6-9:

> "The drugs of the above structured formula, however, possess properties such as a high solubility of 570 mg per ml at a body temperature of 37°C. that can lead to a premature release of the drug from the dosage form. During operation of the dosage forms, the convective motion of the imbibed fluid, and the hydrostatic pressure of the imbibed fluid coupled with the high solubility can result in the premature release of the drugs of the formula."

Therefore, there would have been no reasonable expectation by a person skilled in the art of successfully creating an controlled-release or sustained-release dosage of venlafaxine in view of Theeuwes.

Applicants respectfully submit that the subject matter of claims 9 and 15 would not have been obvious to one of ordinary skill in the art over the prior art. Applicants further submit that the subject matter of claims 16-21 would likewise not have been obvious to one of ordinary skill in the art over the prior art. Accordingly, it is submitted that claims 9 and 15-21 are patentable.

Respectfully Submitted,



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